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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Sherie L. Morrison, et al.
Serial No.	:	08/266,154
Filed	:	June 27, 1994
For	:	RECEPTORS BY DNA SPLICING AND EXPRESSION
Group Art Unit	:	1806
Examiner	:	T. Nisbet

RECEIVED
APR 3 1995
GROUP 1800

March 13, 1995

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION

Sir:

Applicants make this response to the official action mailed on November 1, 1994 in the above-referenced application. The pending claims stand rejected under 35 U.S.C. § 103 as obvious over Cabilly (L, R or 2A) or Boss (2B) in view of Gillies(S). Applicants respectfully traverse this rejection.

As discussed with the Examiner, Boss(2B) is not prior art to applicants' invention. Boss is not prior art for the reasons of record in previously filed papers.

The Gillies patent, U.S. Patent No. 4,663,281, to which the examiner referred in the November 1, 1994 official action was not previously of record in this case; however, the Examiner has communicated it to us. The Gillies patent is a different reference than Gillies(S) which is a journal article. Applicants note that the Gillies patent is not prior art to applicants' invention because its filing date,

March 22, 1984, is after October 19, 1983. Applicants have filed 131 Declarations swearing behind the October 19, 1983 effective date of the Ochi reference, and thus have sworn behind the March 22, 1984 filing date of the Gillies patent.

With respect to the three Cabilly references (L, R, and 2A), the disclosure in two of them is identical. Cabilly(2A) is a U.S. patent, and Cabilly(L) is the EPO patent application claiming priority from Cabilly (2A). The third Cabilly reference, Cabilly(R), is a journal article dated June 1984. This article, like the Gillies patent, is not prior art to applicants' invention because applicants have sworn behind this date in the previously submitted 131 Declarations.

The sum of the foregoing is that two references remain to form the basis of the § 103 rejection, the Cabilly U.S. patent (2A) and the Gillies paper (S). The Examiner asserts that Cabilly's disclosure in view of Gillies makes applicants' invention obvious.

Cabilly discloses double transfection of heavy and light chain genes into bacteria cells. With respect to co-expression of those genes, Cabilly states:

> "When heavy and light chain are coexpressed in the same host, the isolation procedure is designed so as to recover reconstituted antibody. This can be accomplished in vitro as described below, or might be possible in vivo in a microorganism which secretes the IgG chains out of the reducing environment of the cytoplasm." ((emphasis added) Cabilly A, col. 13, lines 19-25.)

Gillies discloses transfection and expression of a heavy chain gene in mammalian cells.

Applicants' invention claims a method for producing a "functional antibody". That method includes co-

transfection and co-expression of both the heavy and light chains in a mammalian cell. Each of the claims requires that the heavy and the light chain be "intracellularly assembled together to form the antibody which is then secreted in a form capable of specifically binding to antigen."

In a genetic engineering case involving the appeal of a PTO action rejecting claims as obvious, the Federal Circuit explained the requirements for a proper analysis under § 103:

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*" In re Vaeck, 20 USPQ2d 1438, 1442 (Fed.Cir. 1991).

There is no suggestion to combine the cited references in order to obtain the instant invention. Neither Cabilly nor Gillies suggests combination with the other. As can be seen from the quote above, while Cabilly asserts that reconstituted antibody can be recovered in vitro, he asserts only that it "might be possible" to recover antibody from co-expressed heavy and light chains in microorganisms. Cabilly does not even go that far with mammalian cells, providing absolutely no suggestion that co-expression is even "possible" in the mammalian cells used in Gillies. Similarly, Gillies provides no suggestion that an exogenous light chain gene could be co-transfected and co-

expressed with the heavy chain gene in vivo as Cabilly says "might be possible" in microorganisms. And, there is absolutely no mention in Gillies that pursuing such a method would yield "functional antibody."

The second requisite for sustaining an obviousness rejection, that a person of skill in the art would have a reasonable expectation of success, is also lacking. In this case, the Cabilly reference in view of Gillies must have lead a person of skill in the art to believe that the mammalian cell would express both exogenous genes, that the two expressed proteins would be assembled together, that the assembled chains would be secreted, and that the secreted chains would be functional in binding antigen. In 1983, if one had been motivated to try co-expression in a mammmalian cell, one might have hoped that the experiment would succeed in producing functional antibody, as did Morrison et al., but one would not have reasonably expected that each of the foregoing steps would be successfully performed resulting in the successful production of functional antibody.* Skill in the art of genetic engineering and immunology is exactly what would have kept an inventor from expecting, as opposed to hoping, to succeed in such a quest.

Applicants offer the following list of information that was available to them and to other persons of skill in the art in 1983, at the time they undertook the experiments that resulted in the instant invention.

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* "Obvious to try" is not the rule in determining whether an invention is obvious. As detailed in applicants' January 3, 1992 Amendment, p. 5, in parent application serial no. 675,106, it is not a basis for rejection that it may be obvious to try applicants' invention. The relevant question is whether the inventors had a reasonable expectation of success.

1. **Cabilly(2A).** As detailed above, Cabilly, despite having disclosed mammalian cells as potential hosts for its expression vectors, only mentions microorganisms when discussing the possibility of recovering antibody in vivo from co-expression of the heavy and light chain genes. As detailed in applicants' amendment, filed on May 15, 1991, p. 6, in parent application serial no. 675,106, Cabilly found that, in vitro, the result of co-expression is essentially the same as the result of expressing heavy and light chain in separate cells. In both instances, Cabilly teaches away from co-expression in the host cell.

2. **Gillies(S).** Applicants were aware of the work underlying the Gillies paper (two of the instant inventors were co-authors of that paper). Gillies detailed work done to identify and understand the operation of genetic elements that acted to enhance or improve the expression of gene segments. A gene coding for an antibody heavy chain was transfected into a mammalian cell. That gene was expressed and heavy chain protein was detected.

Functional antibody could not have been produced with the host cells and vectors disclosed in Gillies. The endogenous light chain had a variable region that was specific for a different antigen than the antigen for which the exogenous heavy chain was specific. Therefore, it would have been impossible for the two chains to assemble together to form a functional antibody.

Thus, a person of skill in the art who read the Gillies article in July 1983 would not have assumed that functional antibody was produced from the transfected heavy chain gene and the endogenous light chain gene. Indeed, in July of 1983, no one had ever made a functional antibody in vivo by transfecting genes into host cells. The accomplishment would have been significant, and not one that the authors would have forgotten to mention. Accordingly, the reasonable person of skill in the art would have assumed that the article disclosed only what actually happened, namely, that the exogenous heavy chain gene was successfully expressed and not that a fully assembled functional antibody capable of binding antigen had been produced.

3. **Oi.** Even if, as in Gillies, one exogenous gene was expressed in the mammalian cell, there would have been no reasonable certainty that two exogenous genes would both be expressed with the resultant chains being assembled and then secreted in functional form.

Prior to the present invention, it was not even believed that one exogenous chain would always be expressed, let alone assembled with a second immunoglobulin chain. In Oi, a mouse myeloma cell supported expression of a transfected immunoglobulin gene. However, a rat myeloma cell line which expresses and secretes an endogenous light chain, when treated in the same manner as the mouse myeloma, did not support expression of a transfected immunoglobulin chain gene.

Prior to the present invention, the art as a whole taught that a non-producing cell would not necessarily

express a transfected exogenous immunoglobulin chain gene. Thus, applicants certainly would not have had a reasonable expectation that such a cell would successfully express, assemble and secrete the product of that first exogenous gene with the product of a second exogenous gene.

4. Even if co-expression of two exogenous genes resulted in the expression, assembly, and secretion of the heavy and light chains, that does not mean that the secreted molecule is a functional antibody. The assembly may not have the complex tertiary structure that is critical to specific binding of antigen. (Morrison 132 Declaration, August 18, 1993)

Given the uncertainties evident from the foregoing list, one of skill in the art would not have had a reasonable expectation of successfully expressing functional antibodies at the time of the invention. Accordingly, applicants' invention is not obvious.

In view of the foregoing, applicants believe that the pending claims are in condition for allowance. Accordingly, allowance of the claims is requested.

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U. S. Postal Service as First Class Mail in an Envelope Addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 13, 1995

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PATENTS

REV. 1/93
Modified PTO 1082
For Other Than A Small Entity

Attorney Docket No. BD1 CIP FWC IV

Applicant(s) : Sherie L. Morrison, et al.

Serial No. : 08/266,154

Filed : June 27, 1994

For : RECEPTORS BY DNA SPLICING AND EXPRESSION

Group Art Unit : 1806

Examiner : T. Nisbet

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GROUP 1800

Hon. Commissioner of Patents
and Trademarks
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TRANSMITTAL LETTER

Sir:

Transmitted herewith: [ ] a Preliminary Amendment; [X] a Response to Examiner's Action; [ ] a Supplemental Amendment; [ ] a substitute Specification; [ ] a Declaration; [ ] a Supplemental Declaration; [ ] a Power of Attorney; [ ] an Associate Power of Attorney; [ ] formal drawings; and [X] Petition for Extension of Time; to be filed in the above-identified patent application.

FEE FOR ADDITIONAL CLAIMS

[X] A fee for additional claims is not required.

[ ] A fee for additional claims is required. The additional fee has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE		ADDITIONAL FEES
TOTAL CLAIMS		-		* =		X	$22	=	$
INDEPENDENT CLAIMS		-		** =		X	$76	=	$
FIRST PRESENTATION OF A MULTIPLE DEPENDENT CLAIM						+	$240	=	$
							TOTAL		$

* If less than 20, insert 20.
** If less than 3, insert 3.

[ ] A check in the amount of $_____ in payment of the filing fee is transmitted herewith.

[X] The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. § 1.16, in connection with the paper(s) transmitted herewith, or credit any overpayment of same, to deposit Account No. 06-1075. A duplicate copy of this transmittal letter is transmitted herewith.

[ ] Please charge $_____ to Deposit Account No. 06-1075 in payment of the filing fee. A duplicate copy of this transmittal letter is transmitted herewith.

EXTENSION FEE

[X] The following extension is applicable to the Response filed herewith; [ ] $110.00 extension fee for response within first month pursuant to 37 C.F.R. § 1.17(a); [X] $370.00 extension fee for response within second month pursuant to 37 C.F.R. § 1.17(b); [ ] $870.00 extension fee for response within third month pursuant to 37 C.F.R. § 1.17(c); [ ] $1,360.00 extension fee for response within fourth month pursuant to 37 C.F.R. § 1.17(d).

[X] A check in the amount of [ ] $110.00; [X] $370.00; [ ] $870.00; [ ] $1,360.00; in payment of the extension fee is transmitted herewith.

[X] The Commissioner is hereby authorized to charge payment of any additional fees required under 37 C.F.R. § 1.17 in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No. 06-1075. A duplicate copy of this transmittal letter is transmitted herewith.

[ ] Please charge the [ ] $110.00; [ ] $370.00; [ ] $860.00; [ ] $1,360.00; extension fee to Deposit Account No. 06-1075. A duplicate copy of this transmittal letter is transmitted herewith.

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Dalene Quiachon-Rosen
Name of Person Signing

Signature of Person Signing